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(54) Title: NOVEL DIAZABICYCLONONENE DERIVATIVES

(57) Abstract: The invention relates to novel 3,9-diazabicyclo[3.3.1]nonene derivatives and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of renin.

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Novel Diazabicyclononene Derivatives

The invention relates to novel compounds of the general formula **I**. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula **I** and especially their use as renin inhibitors in cardiovascular events and renal insufficiency. Furthermore, these compounds can be regarded as inhibitors of other aspartyl proteases and might therefore be useful as inhibitors of plasmepsins to treat malaria and as inhibitors of *Candida albicans* secreted aspartyl proteases to treat fungal infections.

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT_1 and AT_2. Whereas AT_1 seems to transmit most of the known functions of Ang II, the role of AT_2 is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT_1 blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Berkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, **1996**, 489-519; Weber M. A., *Am. J. Hypertens.*, **1992**, *5*, 247S). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney International*, **1994**, *45*, 403; Breyer J. A. *et al.*, *Kidney International*, **1994**, *45*, S156), in the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, **1994**, *28*, 159;

Fouad-Tarazi F. *et al.*, *Am. J. Med.*, **1988**, *84 (Suppl. 3A)*, 83) and myocardial infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, **1992**, *327*, 669).

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, **1992**, *117*, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT_1 receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes to Ang II, whose concentration is dramatically increased by the blockade of AT_1 receptors. This may raise serious questions regarding the safety and efficacy profile of AT_1 receptor antagonists. In summary, renin inhibitors are not only expected to be different from ACE inhibitors and AT_1 blockers with regard to safety, but more importantly also with regard to their efficacy to block the RAS.

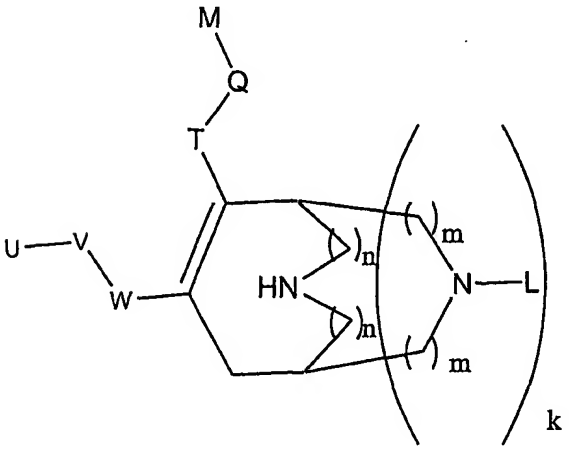
Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, *12*, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, *122*, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, **2000**, *7*, 493; Mealy N. E., *Drugs of the Future*, **2001**, *26*, 1139). Thus, metabolically stable, orally bioavailable and sufficiently soluble renin inhibitors that can be prepared on a large scale are missing and sought. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, **1999**, *6*, 127; Patent Application WO97/09311; Märki H. P. *et al.*, *Il*

Farmaco, **2001**, *56*, 21). However, the development status of these compounds is not known.

The present invention relates to the identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodeling, atherosclerosis, and possibly restenosis are described.

The present invention describes non-peptidic renin inhibitors.

In particular, the present invention relates to novel compounds of the general formula **I**,



Formula **I**

wherein

W is a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in *meta* or *para* position;

V represents $-O-CH_2-CH(OCH_3)-CH_2-O-$; $-O-CH_2-CH(CH_3)-CH_2-O-$; $-O-CH_2-CH(CF_3)-CH_2-O-$; $-O-CH_2-C(CH_3)_2-CH_2-O-$; $-O-CH_2-C(CH_3)_2-O-$; $-O-C(CH_3)_2-$

CH_2-O-; -O-CH_2-CH(CH_3)-O-; -O-CH(CH_3)-CH_2-O-; -O-CH_2-C(CH_2CH_2)-O-; -O-C(CH_2CH_2)-CH_2-O-;

U represents aryl; heteroaryl;

T represents -$CONR^1$-; -$(CH_2)_pOCO$-; -$(CH_2)_pN(R^1)CO$-; -$(CH_2)_pN(R^1)SO_2$-; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

L represents -R^3; -COR^3; -$COOR^3$; -$CONR^2R^3$; -SO_2R^3; -$SO_2NR^2R^3$; -$COCH(Aryl)_2$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, -$OCOR^2$, -$COOR^2$, lower alkoxy, cyano, -$CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -$COOR^2$; -$CONH_2$;

k is the integer 0 or 1;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1, n is the integer 0, and in case n represents the integer 1, m is the integer 0; in case k represents the integer 0, n represents the integer 0;

p is the integer 1, 2, 3 or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

In the definitions of general formula **I** – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl nad isopropyl groups are preferred.

The term **lower alkoxy** refers to a R-O group, wherein R is a lower alkyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl or butenyl.

The term **lower alkinyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkinyl are ethinyl, propinyl or butinyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkylene are ethylene, propylene or butylene.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkylenoxy** refers to a lower alkylene substituted at one end by an oxygen atom. Examples of lower alkylenoxy groups are preferably methylenoxy, ethylenoxy and propylenoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy,

lower alkylenoxy, lower alkylenedioxy, hydroxy, halogen, $-CF_3$, $-NR^1R^{1'}$, $-NR^1C(O)R^{1'}$, $-NR^1S(O_2)R^{1'}$, $-C(O)NR^1R^{1'}$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$ whereby $R^{1'}$ represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl. The cyclopropyl group is a preferred group.

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl group, preferably the phenyl group, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkinyl, lower alkenylene or lower alkylene forming with the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylenedioxy, lower alkylenoxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-NR^1C(O)R^{1'}$, $-NR_1S(O_2)R^1$, $-C(O)NR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$, benzyloxy, whereby $R^{1'}$ has the meaning given above. Preferred substituents are halogen, lower alkoxy, lower alkyl, CF_3, OCF_3.

The term **aryloxy** refers to an Ar-O group, wherein Ar is an aryl. An example of a lower aryloxy group is phenoxy.

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms, if present, can be substituted by a $-COOR^2$ group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings

containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequatly substituted with lower alkyl, lower alkenyl, lower alkinyl, lower alkylene, lower alkenylene, lower alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-N(R^1)COR^1$, $-N(R^1)SO_2R^1$, $-CONR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$, another aryl, another heteroaryl or another heterocyclyl and the like, whereby $R^{1'}$ has the meaning given above.

The term **heteroaryloxy** refers to a Het-O group, wherein Het is a heteroaryl.

The term **sp3-hybridized** refers to a carbom atom and means that this carbon atom forms four bonds to four substituents placed in a tetragonal fashion around this carbon atom.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non toxic to living organisms or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

Compounds of the invention also include nitrosated compounds of the general formula **I** that have been nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulffiydryl condensation) and/or nitrogen. The nitrosated compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For example, known methods for nitrosating compounds are described in U.S. Pat. Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; WO 98/21193; WO 99/00361 and Oae et al, Org. Prep. Proc. Int., 15(3): 165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

The compounds of the general formula **I** can contain two or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts thereof.

The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

A group of preferred compounds are compounds of general formula **I** wherein W, V, U, T, Q, L, and M are as defined in general formula **I** above and wherein

k is 1
n is 0 and
m is 1.

Another group of preferred compounds of general formula **I** are those wherein W, V, U, T, Q, M, k, m, and n are as defined in general formula **I** above and

L represents H; $-COR^{3''}$; $-COOR^{3''}$; $-CONR^{2''}R^{3''}$;

whereby $R^{2''}$ and $R^{3''}$ represent independently lower alkyl, lower cycloalkyl - lower alkyl, which lower alkyl and lower cycloalkyl - lower alkyl groups are unsubstituted or monosubstituted with halogen, cyano, hydroxy, $-OCOCH_3$, $-CONH_2$, -COOH, $-NH_2$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized.

Another group of preferred compounds of general formula **I** above are those wherein W, V, U, L, k, m, and n are as defined in general formula **I** and

T is $-CONR^1-$;
Q is methylene;
M is aryl, heteroaryl.

Another group of even more preferred compounds of general formula **I** are those wherein W, U, L, T, Q, M, k, m, and n are as defined in general formula **I** above and

V represents $-O-CH_2-CH(CH_3)-CH_2-O-$; $-O-CH_2-C(CH_3)_2-CH_2-O-$.

Another group of also more preferred compounds of general formula I are those wherein V, U, T, Q, M, L, k, m, and n are as defined in general formula **I** above and

W represents a 1,4-disubstituted phenyl ring.

Another group of even more preferred compounds of general formula **I** are those wherein W, V, Q, T, M, L, k, m, and n are as defined in general formula **I** above and

U is a mono-, di-, or trisubstituted phenyl or heteroaryl, wherein the substituents are halogen, lower alkyl, lower alkoxy, CF_3.

Especially preferred compounds of general formula **I** are:

(*1R*, *5S*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)propoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*1S*, *5R*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluoro-phenoxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (*1R*, *5S*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)propoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluoro-phenoxy)propoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide.

The compounds of general formula **I** and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. These pharmaceutical compositions containing at least one compound of general formula **I** and usual carrier materials and adjuvants may especially be used for the treatment or prophylaxis of disorders which are associated with a dysregulation of the renin angiotensin system (RAS), comprising cardiovascular and renal diseases. Examples of such diseases are hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure. They can also be used to prevent restenosis after balloon or stent angioplasty, to treat erectile dysfunction, glomerulonephritis, renal colic, and glaucoma. Furthermore, they can be used in the therapy and the prophylaxis of diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppresive agents after organ transplantation, complications of cyclosporin treatment, as well as other diseases presently known to be related to the RAS.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are related to the RAS such as hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppresive agents after organ transplantation, and other diseases which are related to the RAS, which method comprises administering a compound according of formula I to a human being or animal.

The invention further relates to the use of compounds of general formula **I** as defined above for the treatment and/or prophylaxis of diseases which are associated with the RAS such as hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppresive agents after organ transplantation, and other diseases presently known to be related to the RAS.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the RAS such as hypertension, coronary diseases, cardiac insufficiency, renal insufficiency, renal and myocardial ischemia, and renal failure. These medicaments may be prepared in a manner known per se.

The compounds of formula **I** may also be used in combination with one or more other pharmacologically active compounds e. g. with other renin inhibitors, with ACE-inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists, and

neutral endopeptidase inhibitors, for the treatment of disorders as above-mentioned.

All forms of prodrugs leading to an active component comprised by general formula I above are included in the present invention.

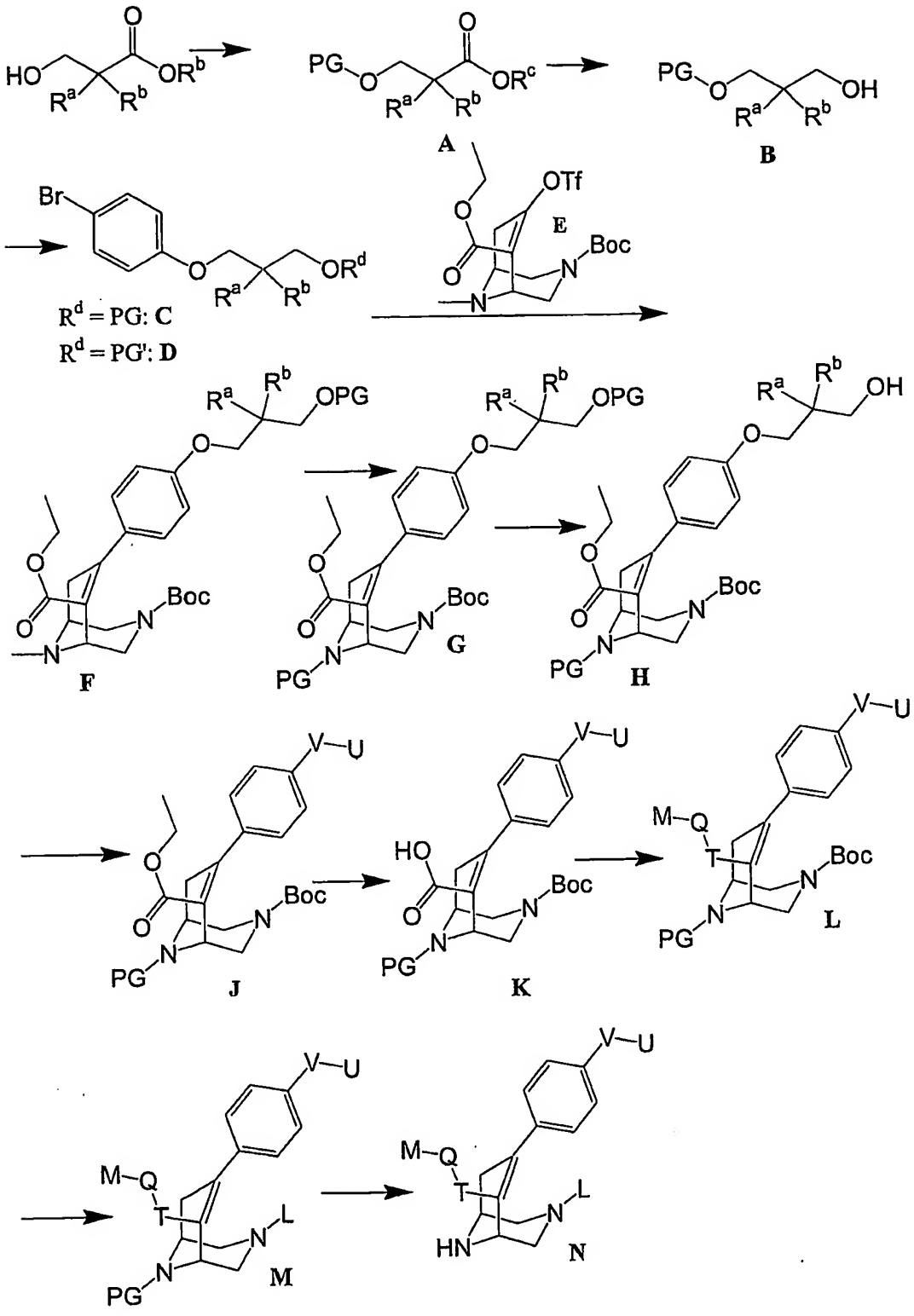
The compounds of general formula **I** can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

Chemistry

The chemistry necessary to prepare the compounds included in general formula **I** might be taken from earlier patent applications, for instance WO 03/093267 or WO 04/002957. The linkers included under V in general formula **I** can be prepared from a commercially available glycerol derivative, from commercially available 3-hydroxy-2,2-dimethylpropionic acid methyl ester, from (*R*)- or (*S*)-3-hydroxy-2-methylpropionic acid (Locher, T.; *et al.*; PCT Int. Appl. WO 0022153 A1 20000420, **2000**; Vogel, G.; *et al.*; *Chemistry and Physics of Lipids*, **1990**, *52*, 99; Seebach, D.; *et al.*; *Helv. Chim. Acta*, **1986**, *69*, 1147), or from (*R*)- or (*S*)-3-hydroxy-2-(trifluoromethyl)propionic acid (Goetzoe, S. P.; et al.; *Chimia*, **1996**, *50*, 20). Also, methyl 1-hydroxy-1-cyclopropane carboxylate or any derivative of lactic acid can be used as starting materials. All these starting materials can be converted into a precuror for the segment V-U by a combination of protecting steps, coupling steps with a phenol derivative, a hydroxyheterocycle, a hydroxycycloalkyl, or a hydroxyheteroaryl (typically *via* a *Mitsunobu* coupling), reductive steps, and/or deprotection steps. For instance a compound of type **A** can be prepared from one of the here above mentionned compound, whereas the R^a- and R^b-groups are as defined in general formula **I** (or precursors to such a group), and $COOR^c$ is a suitable ester, typically a methyl, an ethyl, or a benzyl ester. A reduction of the ester can lead to a compound of type **B**, then a *Mitsunobu* coupling can lead to a compound of type **C**. During the process, the protecting

group (PG) can be cleaved and replaced by a more suitable one (PG') for the following chemistry, leading to a compound of type **D**. Coupling to known vinyl triflate **E** can lead to a bicyclononene of type **F**. Protecting group manipulation can lead to a compound of type **G**, then deprotection to a bicyclononene of type **H**. A next step, for instance a *Mitsunobu* coupling, can lead to a bicyclononene of type **J**, where the V-U segment is completely in place. Saponification can lead to a compound of type **K**, then an amide coupling for instance to a compound of type **L**. Removal of the Boc-protecting group, then alkylation or acylation, can lead to a bicyclononene of type **M**, then deprotection to a desired final compound of type **N**.

Scheme 1


HO
OR^b
R^a
R^b
PG
O
OR^c
A
OH
B
Br
OR^d
R^d = PG: C
R^d = PG': D
OTf
E
Boc
N
OPG
F
G
H
V–U
M–Q
T
L
J
K
M
N
HN

The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical preparations for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid poyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injections are, for example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration.

The pharmaceutical preparations conveniently contain about 1 - 500 mg, preferably 5 - 200 mg of a compound of formula I.

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Example

Abbreviations

ACE	Angiotensin Converting Enzyme
AcOH	Acetic acid
Ang	Angiotensin
aq.	aqueous
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine serum albumine
BuLi	*n*-Butyllithium
DIBAL	diisobutylaluminiumhydride
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
EDC·HCl	Ethyl-*N,N*-dimethylaminopropylcarbodiimide hydrochloride
EIA	Enzyme immunoassay
eq.	equivalent
Et	Ethyl
EtOAc	Ethyl acetate
FC	Flash Chromatography
HOBt	Hydroxybenzotriazol
LC-MS	Liquid Chromatography – Mass Spectroscopy
MeOH	Methanol
org.	organic
PG	protecting group
Ph	Phenyl
RAS	Renin Angiotensin System
rt	room temperature
sol.	Solution
TBAF	tetra-*n*-butyl ammonium fluoride

TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethylsulfonyl
THF	Tetrahydrofuran
TMAD	*N,N,N',N'*-Tetramethylazodicarboxamide

Precursor

(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-2-methylpropionic acid methyl ester (A)

To a mixture of (-)-methyl D-β-hydroxyisobutyrate (5.54 mL, 50 mmol) and imidazole (8.51 g, 125 mmol) in CH_2Cl_2 (150 mL) was added *tert*-butyldiphenylsilyl chloride (19.5 mL, 75 mmol). After stirring for 18 h, the mixture was diluted with CH_2Cl_2 and washed with a saturated aq. NH_4Cl solution and brine. The org. extracts were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Purification by FC (heptane/EtOAc 100:0 → 90:10) yielded the title compound (15.32 g, 86%).

(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-2-methylpropan-1-ol (B)

To a solution of DIBAL (1M in hexane; 113.2 mL, 113.2 mmol), further diluted with THF (400 mL), was added a solution of compound **A** (13.44 g, 37.7 mmol) in THF (150 mL), at –78°C. The solution was stirred for 30 min at –78°C and then MeOH (11.3 mL) was added slowly. The mixture was allowed to warm up. A saturated aq. NH_4Cl solution was added slowly until a granulous solid was formed. The mixture was filtered over a pad of Na_2SO_4. Purification by FC (heptane/EtOAc 98/2 → 95/5→ 90:10→ 80:20) yielded the title compound (11.6 g, 93%). LC-MS; R_t = 1.12, ES+: 329.28.

(*S*)-[3-(4-bromophenoxy)-2-methylpropoxy]-*tert*-butyldiphenylsilane (C)

4-Bromophenol (7.07g, 40.2 mmol) and DIPEA (0.58 mL, 3.3 mmol) were added to a solution of compound **B** (11g, 33.48 mmol) in toluene (335 mL).

Azodicarboxylic dipiperidide (12.67 g, 50.2 mmol) was added, followed by *n*-tributylphosphine (16.52 ml, 67 mmol) at 0°C. The reaction mixture was stirred for 1 h at RT and then 2 h at 60 °C. It was allowed to cool to RT, and then water was added. The mixture was extracted with EtOAc. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (heptane/EtOAc 95/5) yielded the title compound (16.0 g, 99%). LC-MS; R_t = 1.29min.

(*S*)-[3-(4-bromophenoxy)-2-methylpropoxy]-*tert*-butyldimethylsilane (D)

To a solution of compound **C** (13.1g, 27 mmol) in THF (200 mL) was added TBAF (1M solution in THF, 54 mL, 54 mmol) at 0°C. The cooling bath was removed and the reaction mixture was stirred for 2h. AcOEt and a saturated. aq. NH_4Cl solution were added. The aqueous phase was extracted with AcOEt and the org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (heptane/EtOAc 80/20 → 50/50→ 0/100) yielded the title compound (3.79 g, 57%).

To a mixture of the previously obtained compound (3.79 mL, 15.5 mmol) and imidazole (2.63 g, 38.7 mmol) in CH_2Cl_2 (45 mL) was added *tert*-butyldimethylsilyl chloride (3.5 g, 23.2 mmol). After stirring for 3 h, the mixture was diluted with CH_2Cl_2 and washed with a saturated aq. NH_4Cl solution and brine. The org. extracts were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Purification by FC (heptane/EtOAc 98/2 → 95/5) yielded the title compound (3.1 g, 56%). LC-MS; R_t =.1.24min.

1:1 Mixture of (*1R*, *5S*)-7-{(*2S*)-4-[3-(*tert*-butyldimethylsilanyloxy)-2-methylpropoxy]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester and (*1S*, *5R*)-7-{(*2S*)-4-[3-(*tert*-butyldimethylsilanyloxy)-2-methylpropoxy]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (F)

BuLi (1.6M in hexane, 3.2 mL, 5.12 mmol) was added to a sol. of compound **D** (1.8 g, 5 mmol) in THF (4 mL) at –78 °C. The mixture was stirred for 30 min at this temperature, and $ZnCl_2$ (1M in THF, prepared from $ZnCl_2$ dried at 160 °C for 3 h and THF, 6 mL, 6 mmol) was added. The mixture was allowed to warm to rt and a sol. of bicyclononene **E** (0.91 g, 2 mmol) in THF (6 ml), then $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) were added. The mixture was heated to 40 °C and stirred at this temperature for 30 min. A saturated aq. NH_4Cl solution was added. The mixture was extracted with EtOAc (3 times) and washed with brine. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (heptane/AcOEt 50:50 → 0/100 then EtOAc/MeOH 95/5) yielded the title compounds (0.49 g, 41%). LC-MS; R_t = 1.03 ES+: 589.36.

1:1 Mixture of (*1R*, *5S*)-7-{(*2S*)-4-[3-(*tert*-butyldimethylsilanyloxy)-2-methyl-propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester and (*1S*, *5R*)-7-{(*2S*)-4-[3-(*tert*-butyldimethylsilanyloxy)-2-methyl-propoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (G)

A sol. of bicyclononene **F** (0.49 g, 0.83 mmol) and β,β,β-trichloro-*tert*-butylchloroformate (1 g, 4.15 mmol) in CH_2ClCH_2Cl (10 ml) was heated to reflux for 4 h. The mixture was allowed to cool to rt and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 5/95 → 10/90) yielded the title compound (0.40 g, 61%). LC-MS: R_t = 1.33 ES+:777.25.

1:1 Mixture of (*1R*, *5S*)-7-[4-((*2R*)-3-hydroxy-2-methylpropoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester and (*1S*, *5R*)-7-[4-((*2S*)-3-hydroxy-2-methylpropoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (H)

To a solution of bicyclononene **G** (0.40 g, 0.51 mmol) in THF (5 mL) was added TBAF (1M solution in THF, 0.76 mL, 0.76 mmol) at 0°C. The ice bath was removed and the reaction mixture was stirred for 4 h. AcOEt and a saturated. aq. NH_4Cl solution were added. The aqueous phase was extracted with AcOEt and the org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (heptane/EtOAc 30/70 → 50/50→ 2/1) yielded the title compound (0.26 g, 78%).

LC-MS; R_t = 1.95 min.

1:1 Mixture of (*1R*, *5S*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)-propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester and (*1S*, *5R*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (J)

2,3,6-Trifluorophenol (0.07 g, 0.48 mmol) and DIPEA (0.007 mL, 0.04 mmol) were added to a solution of compound **H** (0.26 g, 0.4 mmol) in toluene (5 mL). Azodicarboxylic dipiperidide (0.15 g, 0.6 mmol) was added, followed by tributylphosphine (0.20 ml, 0.8 mmol) at 0°C. The reaction mixture was stirred for 20 min. at RT and then 1 h at 80 °C. The reaction mixture was allowed to cool to RT and water was added. The mixture was extracted with EtOAc. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (heptane/EtOAc 20/80) yielded the title compound (0.28 g, 89%).

LC-MS; R_t = 1.26, ES+: 795.08.

1:1 Mixture of (*1R*, *5S*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)-propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester and (*1S*, *5R*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)-propoxy]phenyl}-3,9-diazabicyclo-

[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (K)

A mixture of bicyclononene **J** (0.28 g, 0.36 mmol) in EtOH (5 ml) and aq. 1M NaOH (3.6 mL, 3.6 mmol)) was stirred at 80 °C for 2.5 h. The mixture was allowed to cool to rt and was acidified with aq 1M HCl. The mixture was extracted with EtOAc (3x) and the org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (heptane/EtOAc 30/70→ 50/50) yielded the title compound (0.20 g 72%). LC-MS: R_t = 1.19; MS-: 765.17.

1:1 Mixture of (*1R*, *5S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)propoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester and (*1S*, *5R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)propoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (L)

A mixture of bicyclononene **K** (0.20 g, 0.26 mmol), (2,3-dichlorobenzyl)cyclopropylamine (0.17 mg, 0.78 mmol), DMAP (0.004 g, 0.06 mmol), DIPEA (0.18 mL, 1.0 mmol), HOBt (0.04 g, 0.32 mmol) and EDC·HCl (0.074 g, 0.39 mmol) in CH_2Cl_2 (5 mL) was stirred for 2 days. EDC.HCl (0.074 g, 0.39 mmol) and DIPEA (0.07 mL, 0.39 mmol) were then added and stirring was continued for 2 days. The mixture was diluted with CH_2Cl_2 and washed with aq. 1M HCl (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (heptane/EtOAc 20:80 → 30/70) yielded the title compound (0.11 g, 44%). LC-MS: R_t = 1.34; ES+: 964.19.

Example

1:1 Mixture of (*1R*, *5S*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)-propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

The bicyclononene **L** (0.11 g, 0.11 mmol) was dissolved in THF (3 mL) and AcOH (0.3 mL) and treated with zinc (0.14 g, 2.2 mmol.). The suspension was stirred for 2 h and filtered through a Titan® HPLC filter. The filtrate was evaporated under reduced pressure and the residue was used in the next step without further purification.

A sol. of the former obtained material (0.08 g, 0.11 mmol) in CH_2Cl_2 (2 mL) was cooled to 0°C. 4M HCl/dioxane (2 mL) was added. After 2.5 h at rt, the solvents were removed under reduced pressure and the residue dried under high vacuum. The title compound was purified by prep.-HPLC. LC-MS: $R_t = 0.80$; ES+: 660.38

The following assay was carried out in order to determine the activity of the compounds of general formula **I** and their salts.

Inhibition of human recombinant renin by the compounds of the invention

The enzymatic in vitro assay was performed in 384-well polypropylene plates (Nunc). The assay buffer consisted of 10 mM PBS (Gibco BRL) including 1 mM EDTA and 0.1% BSA. The incubates were composed of 50 µL per well of an enzyme mix and 2.5 µL of renin inhibitors in DMSO. The enzyme mix was premixed at 4°C and consists of the following components:

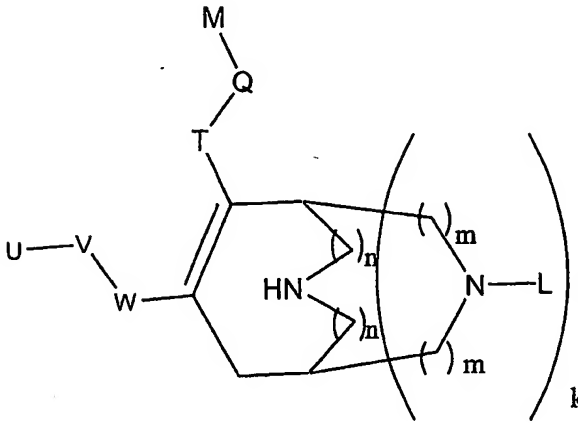
- human recombinant renin (0.16 ng/mL)
- synthetic human angiotensin(1-14) (0.5 µM)
- hydroxyquinoline sulfate (1 mM)

The mixtures were then incubated at 37°C for 3 h.

To determine the enzymatic activity and its inhibition, the accumulated Ang I was detected by an enzyme immunoassay (EIA) in 384-well plates (Nunc). 5 µL of the incubates or standards were transferred to immuno plates which were previously coated with a covalent complex of Ang I and bovine serum albumin (Ang I – BSA). 75 µL of Ang I-antibodies in essaybuffer above including 0.01% Tween 20 were added and a primary incubation made at 4 °C overnight. The plates were washed 3 times with PBS including 0.01% Tween 20, and then incubated for 2 h at rt with an antirabbit-peroxidase coupled antibody (WA 934, Amersham). After washing the plates 3 times, the *peroxidase substrate* ABTS (2.2'-azino-di-(3-ethyl-benzthiazolinsulfonate), was added and the plates incubated for 60 min at room temperature. After stopping the reaction with 0.1 M citric acid pH 4.3 the plate was evaluated in a microplate reader at 405 nm. The percentage of inhibition was calculated of each concentration point and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC_{50}). The IC_{50}-values of all compounds tested are below 100 nM. However selected compounds exhibit a very good bioavailibility and are metabolically more stable than prior art compounds.

Claims

1. Compounds of the general formula I



General formula I

wherein

W is a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in *meta* or *para* position;

V represents –O-CH_2-$CH(OCH_3)$-CH_2-O: -O-CH_2-$CH(CH_3)$-CH_2-O-; -O-CH_2-$CH(CF_3)$-CH_2-O-; -O-CH_2-$C(CH_3)_2$-O-; -O-$C(CH_3)_2$-CH_2-O-; -O-CH_2-$CH(CH_3)$-O-; -O-$CH(CH_3)$-CH_2-O-; -O-CH_2-$C(CH_2CH_2)$-O-; -O-$C(CH_2CH_2)$-CH_2-O-;

U represents aryl; heteroaryl;

T represents -$CONR^1$-; -$(CH_2)_pOCO$-; -$(CH_2)_pN(R^1)CO$-; -$(CH_2)_pN(R^1)SO_2$-; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

L represents -R^3; -COR^3; -$COOR^3$; -$CONR^2R^3$; -SO_2R^3; -$SO_2NR^2R^3$;

-$COCH(Aryl)_2$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, -$OCOR^2$, -$COOR^2$, lower alkoxy, cyano, -$CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represents hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -$COOR^2$; -$CONH_2$;

k is the integer 0 or 1;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1, n is the integer 0, and in case n represents the integer 1, m is the integer 0; in case k represents the integer 0, n represents the integer 0;

p is the integer 1, 2, 3 or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

2. Compounds of general formula I according to claim 1 wherein W, V, U, T, Q, L, and M are as defined in general formula I and

k is 1
n is 0
m is 1,

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

3. Compounds of general formula I according to claim 1 wherein W, V, U, T, Q, M, k, m, and n are as defined in general formula I and

L represents -$COR^{3''}$; -$COOR^{3''}$; -$CONR^{2''}R^{3''}$;

$R^{2''}$ and $R^{3''}$ represent independently lower alkyl; lower cycloalkyl - lower alkyl, which lower alkyl and lower cycloalkyl-lower alkyl are undubstituted or mono-substituted with halogen, -CN, -OH, -$OCOCH_3$, -$CONH_2$,-COOH, or -NH_2, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized,

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

4. Compounds of general formula I according to claim 1 wherein W, V, U, L, k, m, and n are as defined in general formula I and

T represents -$CONR^{1}$-;

Q represents methylene;

M represents aryl, heteroaryl;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

5. Compounds of general formula I according to claim 1 wherein W, U, L, T, Q, M, k, m, and n are as defined in general formula I and

V represents $-O-CH_2-CH(CH_3)-CH_2-O-$; $-O-CH_2-C(CH_3)_2-CH_2-O-$;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

6. Compounds of general formula I according to claim 1 wherein V, U, T, Q, M, L, k, m, and n are as defined in general formula I and

W represents a 1,4-disubstituted phenyl ring,

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

7. Compounds of general formula I according to claim 1 wherein W, V, Q, T, M, L, m, and n are as defined in general formula I and

U is a mono-, di-, or trisubstituted phenyl or heteroaryl, whereby the substituents are halogen, lower alkyl, lower alkoxy, CF_3

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

8. The compounds according to any one of claims 1 to 7 selected from the group consisting of

(*1R*, *5S*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)propoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide;

(*1S*, *5R*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluoro-phenoxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide;

a mixture of (*1R*, *5S*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluorophenoxy)propoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*2S*)-2-methyl-3-(2,3,6-trifluoro-phenoxy)propoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide.

9. Pharmaceutical compositions containing at least one compound of any ones of claims 1 to 8 and usual carrier materials and adjuvants for the treatment or prophylaxis of disorders which are associated with a dysregulation of the renin-angiotensin system (RAS), comprising cardiovascular and renal diseases, hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases known to be related to the RAS.

10. A method for the treatment or prophylaxis of diseases which are related to the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases which are related to the RAS, which method comprises administering a compound according to any one of claims 1 to 8 to a human being or animal.

11. The use of compounds according to any one of claims 1 to 8 for the treatment or prophylaxis of diseases which are associated with the RAS comprising hypertension, congestive heart failure, pulmonary hypertension, cardiac insufficiency, renal insufficiency, renal or myocardial ischemia, atherosclerosis, renal failure, erectile dysfunction, glomerulonephritis, renal colic, glaucoma, diabetic complications, complications after vascular or cardiac surgery, restenosis, complications of treatment with immunosuppressive agents after organ transplantation, and other diseases known to be related to the RAS.

12. The use of one or more compounds of any one of claims 1 to 8 in combination with other pharmacologically active compounds comprising ACE inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists, and neutral endopeptidase inhibitors, for the treatment of disorders as set forth in any one of claims 9 to 11.